

Selective Sweeps

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ABSTRACT For almost 20 years, many inference methods have been developed to detect selective sweeps and localize the targets of directional selection in the genome. These methods are based on population genetic models that describe the effect of a beneficial allele (e.g., a new mutation) on linked neutral variation (driven by directional selection from a single copy to fixation). Here, I discuss these models, ranging from selective sweeps in a panmictic population of constant size to evolutionary traffic when simultaneous sweeps at multiple loci interfere, and emphasize the important role of demography and population structure in data analysis. In the past 10 years, soft sweeps that may arise after an environmental change from directional selection on standing variation have become a focus of population genetic research. In contrast to selective sweeps, they are caused by beneficial alleles that were neutrally segregating in a population before the environmental change or were present at a mutation-selection balance in appreciable frequency.

KEYWORDS genetic hitchhiking; selective sweeps; background selection; demography

WHEN a strongly advantageous mutation occurs and spreads in a population by directional selection, it is inevitable that the frequency of linked neutral (or weakly selected) variants increases. In a seminal paper entitled *The hitch-hiking effect of a favorable gene*, Maynard Smith and Haigh (1974) described this process and termed it *genetic hitchhiking*. They showed that, in very large populations, a single hitchhiking event can reduce genetic variation near the site of selection in the genome.

The hitchhiking effect can most easily be envisioned in nonrecombining organisms (bacteria), in which it was actually first studied and called *periodic selection* (Atwood *et al.* 1951). Suppose a new, selectively favored, mutation arises in a haplotype that carries a given set of neutral nucleotide variants. If the favored mutation goes to fixation, the neutral variants linked to the selected mutation will also spread (“hitchhike”) to fixation, while the other variants in the region will get lost. As a consequence, at the time of fixation of the beneficial allele, genetic variation on the entire haplotype is completely eliminated. However, as Maynard Smith and Haigh (1974) demonstrated, in the presence of recombina-

tion, the size of the region of reduced variation may be limited to a relatively small fraction of the genome.

The basic hitchhiking model analyzed by Maynard Smith and Haigh (1974) is shown in Figure 1. Initially, when a beneficial allele arises by mutation there are three different haplotypes present in the population: two of them are polymorphic at the focal neutral locus (with alleles A and a) and monomorphic at a selected locus nearby, while the third haplotype carries the beneficial allele at the selected locus and one of the neutral alleles (here A) at the other locus. After fixation of the beneficial allele, only one haplotype exists in the population if no recombination event has occurred between the neutral and selected loci (lower left side of the panel); in this case, variation at the neutral locus is eliminated at the time of fixation through the hitchhiking effect. In contrast, if recombination has occurred during the fixation process of the beneficial allele, the neutral locus remains polymorphic, and thus two haplotypes are present in the population (lower right side). After fixation of the beneficial allele, the neutral locus remains polymorphic if it can escape hitchhiking. The chance of this happening increases with the recombination rate c and with the time available for recombination to occur. The latter is proportional to $1/s$, where s is the selection coefficient of the beneficial allele. Combining this suggests that c/s is the crucial parameter of Maynard Smith and Haigh’s hitchhiking model and that this parameter determines the size of the region of reduced variation in the genome of sexual species.

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Basic hitchhiking model

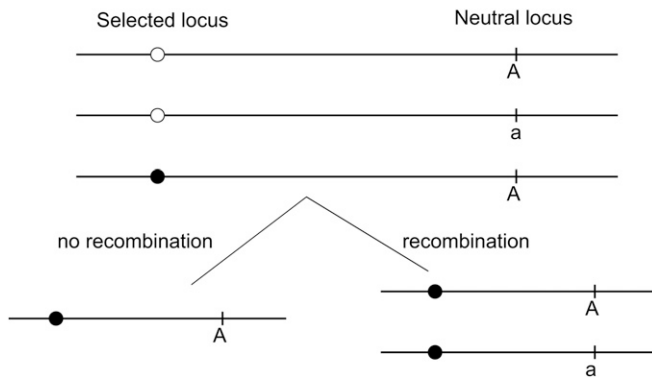


Figure 1 Basic hitchhiking model. The upper part of the figure shows the three haplotypes present in a population when a beneficial mutation (filled circle) occurs at the selected locus. The wildtype allele at the selected locus is indicated by an open circle. At the neutral locus two alleles A and a are present. The haplotypes after the fixation of the beneficial allele are depicted in the lower part of the figure. If no recombination occurs during the fixation process one haplotype is present (left side). With recombination the neutral locus stays polymorphic and two haplotypes remain (right side).

The hitchhiking model was stimulated by Lewontin's (1974) observation that allozyme variability levels are only weakly related to population size, which contradicts the predictions of the neutral theory. Maynard Smith and Haigh's analysis suggests that the observed pattern of genetic variability in a species would depend more on the frequency of hitchhiking events than genetic drift determined by effective population size. Readers further interested in the historical context of the hitchhiking model, and the study of neutral variation linked to selection in general, are referred to the recent review by Charlesworth and Charlesworth (2018).

In the 1970s, population geneticists were conscious that selection at a locus may have effects on another locus, but were thinking almost entirely about fitness interactions between two selected loci, and not about effects when the variants at one locus are neutral (D. Charlesworth, personal communication). Maynard Smith and Haigh's work was therefore original and exciting for the community or provoked strong rebuttals (see Ohta and Kimura 1975).

Genetic hitchhiking, or, in other words, the study of selection via linked neutral variation, has become an important concept in evolutionary genetics, because the observed patterns of neutral variation may be used to infer where selective events (whose genomic location is usually unknown) have occurred along the genome. This may then lead to the identification and characterization of genes that are important in adaptation, or of alleles that cause fitness differences between individuals or populations. Identifying selection events along the genome through genetic hitchhiking may also be useful for fine-scale analysis in other mapping studies (e.g., of quantitative trait loci). Furthermore, evolutionary rates, such as rates of adaptive substitutions, can be inferred from such analyses as well as estimates of the strength of selection.

In this paper, I will briefly describe the extensions of the basic hitchhiking model and its application to statistical tools for detecting positive selection in the genome from patterns of variation at neutral sites, which in the meantime have developed to a large volume.

Selective Sweeps vs. Background Selection

The hitchhiking effect was revisited in the late 1980s to explain patterns of reduced variation in restriction-fragment-length-polymorphism data, which were collected in Charles H. Langley's laboratory. These patterns were found in genomic regions of low recombination rates around centromeres and telomeres (Aguadé *et al.* 1989; Stephan and Langley 1989) and also on the fourth chromosome of *Drosophila* (Berry *et al.* 1991). Begun and Aquadro (1992) corroborated these results by showing that levels of DNA variation correlate with recombination rates across much of the *D. melanogaster* genome, whereas average divergence to *Drosophila simulans* was hardly affected by recombination. Given these data, the deterministic hitchhiking model of Maynard Smith and Haigh (1974) was extended by Kaplan *et al.* (1989), who analyzed a stochastic version of the process (including genetic drift) by means of coalescent theory. Furthermore, Stephan *et al.* (1992) and Wiehe and Stephan (1993) studied the recurrent hitchhiking case using the diffusion equation method. In the recurrent case, hitchhiking events occur at multiple loci across the genome. Alternative approximations of the hitchhiking model were provided by Barton (1998) and Gillespie (2000).

The concept of genetic hitchhiking is now very broadly used in population genetics and describes any situation in which changes in allele frequencies caused by selection affect the frequencies of neutral variants at linked sites in the genome. This includes any type of selection that is sufficiently strong. At the same time, and more specifically, for genetic hitchhiking caused by directional selection (as considered by Maynard Smith and Haigh) the term *selective sweep*, which was introduced by Berry *et al.* (1991), is now generally used.

Since the publication of the paper entitled *The effect of deleterious mutations on neutral variation* by Charlesworth *et al.* (1993), two major population genetic models have competed in explaining the observed reduction of nucleotide variation in genomic regions of reduced recombination rates. According to both models, the level of neutral (or nearly neutral) variation can be reduced below classical neutral expectation by selection against the steady input of deleterious mutations (so-called *background selection*) or by recurrent selective sweeps. The discovery of reduced levels of variation in genomic regions of restricted crossing-over, and the ensuing controversy over its interpretation, initiated an important phase in molecular population genetics. Since these observations were not limited to *Drosophila*, but were also found – at least to some extent – in other organisms such as humans (Nachman *et al.* 1998; Hellmann *et al.* 2003) and plants (Kraft *et al.* 1998; Stephan and Langley 1998), the development

Box 1 Overview of Models of Selective Sweeps and Statistical Tests for Sweep Detection

Model of

- a single selective sweep: describes the effect of a strongly beneficial allele on linked neutral variation (see Figure 1)
- recurrent selective sweeps: describes the cumulative effect of single sweeps occurring sequentially at multiple loci along the genome
- competing selective sweeps: like the model of recurrent selective sweeps but sweeps may occur simultaneously and therefore interfere with each other
- soft sweep: involves beneficial alleles present initially (at the time of environmental change) as >1 copy

Frequently used tests for sweep detection:

- CLR test: detects a single selective sweep (without controlling for demography)
- GOF test: used in combination with the CLR test to control for demography
- SweepFinder: CLR test that is applicable to the whole genome and also controls for background selection
- SweeD test: computationally advanced test based on the SweepFinder algorithm
- iHS test: haplotype-based test that detects an ongoing selective sweep

of new methods distinguishing the relative contributions of background selection and selective sweeps was a major activity in those years (until ~ 2000).

Despite substantial efforts from many theorists and empiricists, fundamental questions on the relation of background selection and selective sweeps are still open. However, since these issues are not a major subject here, the reader is referred to recent work of Comeron (2014, 2017) and Elyashiv *et al.* (2016). In this article, I describe a major shift in focus of the basic model of a selective sweep to models of selective sweeps with an emphasis on an application to data from genomic regions of normal recombination. This shift that occurred ~ 2000 is accompanied by the advent of population genomics, which allowed collecting large sets of polymorphism data along the entire genome of recombining species (including regions of normal recombination rates). In the following, complexities, such as demography, population structure, and confounding selection regimes, are introduced successively into the basic model of Maynard Smith and Haigh (1974), to make the models more realistic and applicable to data. An overview of the various models and statistical methods is provided in Box 1.

Single Selective Sweeps

The simplest case: a single selective sweep in a local population of constant size

We consider a locus under positive directional selection in a local population. We assume that a beneficial allele occurs at some time in the past and goes to fixation. The sudden occurrence of this allele may be caused by mutation, migration from another subpopulation or may be due to a very rare allele in the standing variation after an environment change. According to Maynard Smith and Haigh's model, nucleotide diversity vanishes in recombining chromosomal regions at the site of selection immediately after the fixation of the

beneficial allele and increases as a function of the ratio of the recombination rate c (between the neutral and selected sites) and the selection coefficient s . For finite populations of large constant size, the results obtained by coalescent (Kaplan *et al.* 1989) and diffusion (Stephan *et al.* 1992) approximations are in excellent agreement with Maynard Smith and Haigh's deterministic predictions. This is because the derivations in these aforementioned papers require that selection is very strong ($N_e s \gg 1$), such that fixation occurs very quickly relative to one unit of the time scale of the effective population size N_e , which corresponds to N_e generations.

Later research found two other important signatures of the selective sweep model: (i) shifts in the site frequency spectrum (SFS) of polymorphisms such as an excess of low-frequency (Braverman *et al.* 1995) and high-frequency (Fay and Wu 2000) derived alleles, and (ii) characteristic patterns of linkage disequilibrium (LD), such as an elevated level of LD during the fixation process and a complete break-down of LD across the selected site after fixation (Kim and Nielsen 2004; Stephan *et al.* 2006).

These features of the selective sweep model have been used to infer signatures of strong positive directional selection in the genomes of recombining organisms. Kim and Stephan (2002) developed a composite-likelihood ratio (CLR) test to detect local reductions of nucleotide diversity along a recombining chromosome, and to predict the strength and location of the target of selection. The CLR test compares the probability of the observed polymorphism data under the standard neutral model (*i.e.*, constant population size) with the probability of the data under the model of a selective sweep. Since the null and the alternative hypotheses in the CLR test are explicitly modeled, the interpretation of the test results is straightforward. On the other hand, it is important to note that the null hypothesis of the test is formulated based on the standard neutral model. This means that a violation of the assumptions of the null hypothesis may influence the

results and favor the alternative hypothesis. Therefore, the application of the CLR test is not appropriate for detecting selective sweeps when severe demographic events have occurred in the history of a population. In this case an additional approach may be used to distinguish sweeps from demography (in particular bottlenecks), which is described in the next section.

The first genome scans for selective sweeps were performed on humans (Akey *et al.* 2002), *D. melanogaster* (Harr *et al.* 2002; Schlötterer 2002; Glinka *et al.* 2003; Orengo and Aguadé 2004), and mice (Ihle *et al.* 2006). The data consisted of large numbers (~100) of mostly randomly chosen loci along chromosomal regions of normal recombination rates. Both microsatellite and nucleotide variation were investigated. In all these studies, a surprisingly large number of loci showed signatures of selective sweeps, such as reduced variation or high differentiation between subpopulations. This immediately suggested that not all of these signatures were due to directional selection. As the populations that were examined were mostly derived, demographic factors (in particular bottlenecks during the colonization of new habitats) needed to be taken into account.

Selective sweep in a population undergoing demographic changes

Jensen *et al.* (2005) showed that the CLR test is not robust in the case of recent strong bottlenecks. Under this scenario, the false-positive rate may be as high as 80%, depending on the severity of the bottleneck. They proposed to use in addition to the CLR test a goodness-of-fit (GOF) approach to distinguish between the true positives that come from the rejection of the standard neutral scenario because of a sweep, and the false positives that come from the rejection of the standard neutral model due to demography. The combined CLR and GOF tests have been used extensively to analyze subgenomic data, *i.e.*, data from local genomic regions (reviewed elsewhere, *e.g.*, Pavlidis *et al.* 2008 and Stephan 2010a).

The availability of whole-genome or chromosome-wide SNP data, mainly from the HapMap Project (International HapMap Consortium 2003), motivated Nielsen *et al.* (2005) to develop a more general method (called SweepFinder) that could also be applied to genome-wide data. This test is based on the CLR approach of Kim and Stephan (2002). However, it differs from the latter in that the null hypothesis is not derived from the standard neutral model, but estimated from the empirical background distribution of the data. It therefore may take deviations from the constant-population size neutral model into account, at least to some extent.

Although SweepFinder may be robust against some demographic scenarios that have been investigated by Nielsen *et al.* (2005), simulations have shown that this does not hold in general, especially in cases of recent severe bottlenecks (Pavlidis *et al.* 2008). We have therefore incorporated LD information into the methods for detecting targets of positive directional selection that thus far have been based on the SFS

alone. As suggested by the simulations of Jensen *et al.* (2007), the statistic ω proposed by Kim and Nielsen (2004) may be very powerful in distinguishing demographic from selective scenarios. Indeed, analyzing the correlation of SweepFinder and ω has enabled us to separate selection from demography even for rather deep bottlenecks (Pavlidis *et al.* 2010).

The more recent developments have focused on advancing the computational power of the sweep tests. The approach of Boitard *et al.* (2009), which is based on hidden Markov models and machine-learning, appears to perform better than the original methods by Kim and Stephan (2002) and Nielsen *et al.* (2005) in the case of bottlenecks. A computationally advanced CLR-based test is SweeD (Pavlidis *et al.* 2013). It includes a demographic model with an arbitrary number of instantaneous changes in population size and is applicable to large datasets. Another recent sweep test is OmegaPlus, which is a very fast algorithm that utilizes only LD information (Alachiotis *et al.* 2012). Finally, the algorithm just published by Akbari *et al.* (2018) claims that it can pinpoint the causative mutation of a single sweep in a large genomic region without prior knowledge of demography or functional annotations of mutations.

Selective sweep in a substructured population

In a panmictic population, the fixation of a strongly advantageous allele may occur very rapidly on the time scale of the effective population size N_e (Kaplan *et al.* 1989; Stephan *et al.* 1992). In contrast, in a subdivided population this process may take much longer, especially when migration is reduced (Slatkin and Wiehe 1998; Whitlock 2003; Kim and Maruki 2011). As a consequence, the hitchhiking process may usually not be complete, but ongoing (in the total population). Incomplete sweeps are often observed in humans (Nielsen *et al.* 2007), because in this case limited migration and also strong population size expansion slow down fixation of beneficial alleles.

Theoretical predictions of the effect of sweeps on genetic differentiation have been obtained by several authors. In the case of reduced migration a sweep in a subdivided population due to sequential fixation of the beneficial allele increases differentiation if neutral variation near the selected site is relatively homogenous across subpopulations initially (Slatkin and Wiehe 1998; Bierne 2010). On the other hand, if the subpopulations are initially differentiated, hitchhiking of the same beneficial allele will decrease F_{ST} (Santiago and Caballero 2005).

The CLR method has been extended to substructured populations by Chen *et al.* (2010). However, population size changes have not been considered in this approach (called XP-CLR test).

If a selective sweep is ongoing, the hitchhiking haplotype is expected to be rather long due to strong LD (see above). This feature of the hitchhiking effect has been exploited in model-free, haplotype-based tests, such as the iHS test (Sabeti *et al.* 2002; Voight *et al.* 2006; Tang *et al.* 2007). The decay of the

haplotype length due to recombination is slower if the haplotypes are driven by positive selection.

Yet another class of tests compares polymorphism data from two or more subpopulations to find evidence for local adaptation. Different selection pressures between demes may lead to strong genetic differentiation that can be measured by F_{ST} . Bayesian approaches have been used to reveal genomic regions that have experienced recent strong positive directional selection and hence large F_{ST} , although these methods may lead to overestimation of F_{ST} and should only be used after careful analysis of the population structure (Beaumont and Balding 2004; Foll and Gaggiotti 2008; Riebler *et al.* 2008).

Joint inference of demographic and selective forces

In the inference of selective sweeps described above, we have assumed that the demographic history of a population is not confounded by forms of weak selection that concern the whole genome. This, however, is only a rough approximation, especially for populations with large effective size. For this reason it would be desirable to infer the demographic and selective history jointly, which means that all selective processes and demography are analyzed simultaneously. In the case of background selection and selective sweeps, both of which reduce levels of genetic diversity and are hard to distinguish (particularly in regions of low recombination, Stephan 2010b), an early attempt has been made to study their joint effects (Kim and Stephan 2000). However, progress along this line has been made only very recently. Comeron (2014) proposed background selection as a sensible null hypothesis for investigating the presence of other forms of linked selection, such as directional selection, and Elyashiv *et al.* (2016) modeled the joint effects of background selection and selective sweeps. Both applied their approaches to *D. melanogaster* data, utilizing the detailed genetic maps available for this species. Furthermore, Huber *et al.* (2016) extended SweepFinder to detect selective sweeps while controlling for background selection.

Selective Sweeps at Multiple Loci

In this section, I will first discuss recurrent selective sweeps; *i.e.*, sweeps that occur sequentially at multiple selected loci, because at any time at most one beneficial allele is assumed to be on the way to fixation. Then I will describe the models on competing sweeps, also called evolutionary traffic; *i.e.*, we will allow for interference between simultaneously occurring sweeps.

Recurrent selective sweeps

Given the relatively high rate of selective sweeps at individual loci for species with large effective population size such as *D. melanogaster*, the question arises whether a model of recurrent sweeps is more appropriate in describing the data than a model of single sweeps at individual loci. The model of selective sweeps at individual loci described above can be extended to multiple loci in a straightforward way by assuming

that sweeps occur along the genome independently according to a time-homogeneous Poisson process at rate ν per site per generation (Kaplan *et al.* 1989). Using this assumption, Wiehe and Stephan (1993) derived a simple formula quantifying the expected level of equilibrium nucleotide diversity, π , along the genome given the recombination rate, ρ , per generation per nucleotide site and the intensity of selection, $\alpha = 2N_e s$, where s is the average selection coefficient of strong beneficial substitutions in the genome:

$$\pi = \pi_0 \frac{\rho}{\rho + \kappa \alpha \nu}. \quad (1)$$

Here, π_0 is the neutral equilibrium level of diversity and $\kappa = 0.075$ is a constant.

In contrast to the single-sweep model, simulations have shown that the targets of selection are difficult to localize based on this recurrent hitchhiking model (Pavlidis *et al.* 2010). The frequency of advantageous substitutions, on the other hand, can be estimated rather accurately (Jensen *et al.* 2008). The above equation suggests that the parameters α and ν cannot be estimated individually but only as a product (Stephan 1995). This would mean that frequent weak beneficial substitutions and rare strongly selected substitutions predict similar average effects on linked neutral variation. However, utilizing the insight that rare strong selection increases the variance of the common summary statistics of nucleotide heterozygosity along the genome relative to ubiquitous weak selection, the ABC approach of Jensen *et al.* (2008) allows distinguishing between these alternatives and the estimation of α and ν separately.

Campos *et al.* (2017) considered models of both background selection and recurrent selective sweeps, including gene conversion in addition to crossing-over. Using *Drosophila* data, they showed that gene conversion may have large effects on the parameter estimates of these models.

The effect of recurrent selective sweeps on the SFS of neutral polymorphisms has been analyzed by Kim (2006). He showed that the excess of high-frequency derived alleles, a hallmark of single sweeps (Fay and Wu 2000; Przeworski 2002), disappears under recurrent selective sweeps.

Competing selective sweeps

Next, I will discuss the case in which selective sweeps along the genome do not occur sequentially, but interfere with each other. Such evolutionary traffic of interfering positive fixations has been described by several authors (Barton 1995; Kirby and Stephan 1996; Yu and Etheridge 2010; Bossert and Pfaffelhuber 2016), but the impact on linked neutral variation is not well understood. To my knowledge, only two studies have modeled genetic hitchhiking in the presence of interference between partially linked beneficial alleles on their way to fixation. Using full-forward simulations and analytical approximations, Kim and Stephan (2003) found that interference between linked beneficial alleles causes a reduction of their fixation probability. The hitchhiking effect on neutral

variation for a given substitution also decreases slightly due to interference. As a result, the strength of recurrent selective sweeps is weakened. However, this effect is significant only in chromosomal regions of low recombination rates (e.g., around the centromeres in *Drosophila*). Therefore, the results on recurrent sweeps derived for the case that at most one beneficial allele is on the way to fixation are still largely valid, at least in chromosomal regions of normal recombination.

Chevin *et al.* (2008) explicitly modeled the case of two closely linked, selected loci, and one neutral locus for infinitely large populations using ordinary differential equations. Similar to Kim and Stephan (2003), they also observed a weaker hitchhiking effect than for a single sweep of comparable selection strength. Most interestingly, the interference of both fixation processes may lead for some initial conditions and, in some parameter ranges, to an excess of intermediate-frequency variants in the genomic region between the selected sites, which may be interpreted falsely as a sign of balancing selection. The reason is that, when the beneficial alleles arise on different chromosomes, they need to recombine into one chromosome to go to fixation, which can take a long time and thus increase genetic variation. This phenomenon is related to the case of associative overdominance (Frydenberg 1963; Zhao and Charlesworth 2016), which was the first process studied in which selection on sites in genomes affects neutral variants (Sved 1968; see also the review by Charlesworth and Charlesworth 2018).

Soft Sweeps

As explained above, a selective sweep arises if a beneficial allele occurs at some recent time in the past and goes to fixation. The sudden occurrence of the beneficial allele may be caused by mutation, migration from another subpopulation, or may be due to a very rare allele in the standing variation after an environmental change. In contrast, a different case of linked selection occurs if the driving favorable allele is from the standing variation, but not in very low frequency when the environmental shift occurs. This may lead to a so-called *soft sweep* (Hermisson and Pennings 2005).

This process is different from a selective sweep because, in a soft sweep, the driving beneficial allele was present in a population before the environment changed; *i.e.*, it was segregating neutrally or at an appreciable frequency under a mutation-selection balance, and was thus present on more than one haplotype. Several authors (Orr and Betancourt 2001; Innan and Kim 2004; Hermisson and Pennings 2005; Przeworski *et al.* 2005) examined the frequency at which an allele must be segregating before the shift in selection pressure such that a soft sweep arises. This frequency depends on the size of several relatively unknown parameters, which makes it difficult to predict theoretically how often soft sweeps occur.

In practice, another problem is to distinguish soft sweeps from classical selective sweeps in the data because of multiple confounding effects. Jensen (2014) discussed a widely cited

example of selection on standing variation describing this point, the *Eda* locus in sticklebacks (Colosimo *et al.* 2005):

With evidence for selection reducing armor plating in freshwater populations compared with the ancestral heavily plated marine populations, the authors sequenced marine individuals to estimate the allele frequency of the freshwater adaptive low plate morphs, with estimates ranging from 0.2 to 3.8%. While the low plate morph is likely deleterious in marine populations (potentially suggesting that it is at mutation-selection balance), migration from the marine environment may indeed serve as an important source of variation for local freshwater selective sweeps. However, as noted by the authors, it is difficult to separate this hypothesis from that of local freshwater adaptation on new mutations, followed by back migration of locally adapted alleles into the marine population (Jensen 2014).

On the other hand, Hermisson and Pennings (2017) reported cases of soft sweeps in various organisms, including eukaryotes. Perhaps the best example is lactase persistence in humans. At the lactase gene *LCT*, more than a single haplotype has been found in some local African populations, which would indeed be indicative of a soft sweep.

Some authors have pushed the idea that soft sweeps may also arise from multiple adaptive mutations (where the mutations are meant to occur at the same nucleotide site). As I discussed elsewhere (Stephan 2016), this would require extremely large effective population sizes and/or nucleotide mutation rates. Readers interested in this model and its applications to data are referred to the work of Petrov and colleagues, who claim to have evidence for soft sweeps from multiple beneficial mutations (e.g., Karasov *et al.* 2010).

Conclusions

There has been much progress in identifying selective sweeps underlying a range of adaptations. In particular, in organisms with large effective population sizes, such as *D. melanogaster*, the evidence for sweeps is quite striking (reviewed in Stephan 2010a). There is also agreement that sweeps may be detected with reasonably high confidence if the demographic history of a population is taken into account, except in the case of some complex demographies such as recent severe population size bottlenecks (Pavlidis *et al.* 2010). On the experimental side, however, the search for causative nucleotide changes that led to selective sweeps has started only recently (Saminadin-Peter *et al.* 2012; Voigt *et al.* 2015; Catalán *et al.* 2016), although sweep mapping may lead to quite accurate identification of the targets of selection. Clearly, there is a lot of room for future research activities in this latter area. One should keep in mind that all of the methods discussed can only create hypotheses about the regions under selection, which should be tested by manipulative experiments.

On the theoretical side, although the theoretical advances in the detection of positive selection in genomes are impressive, some aspects need further attention. First, the evolution of interacting selective sweeps (the traffic model) is still

largely unexplored. We still lack predictions of this model about the distribution of variation across the genome around the selected sites and on the SFS. Second, efforts of estimating demography and weak selection jointly have so far not led to computer programs that are applicable to data. Third, population subdivision is not well incorporated into the sweep approaches yet (except in F_{ST} -based methods such as BayeScan), but the mathematical treatment of this case is very difficult (Greven *et al.* 2016).

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